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A Review On Pharmacological Effects Of Bilwa: *Aegle Marmelos L.* (Rutaceae)

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ABSTRACT

This article provides a review on the pharmacological effects of *Aegle marmelos*. It is belonging to Rutaceae family. The *Aegle marmelos* is also known as Bael, Bilwa and wooden apple plant. It contains various bioactive components in leaves, flowers, fruits, wood, root, and bark which has different biological activities and high therapeutic importance. The phytochemical compounds which are isolated from the *Aegle marmelos* are Coumarins (Marmelosin, marmesin, imperatorin), alkaloids (Aeglin, aegelenine), Tannins (skimmianine), Carotenoids and seed oils and other miscellaneous compounds. The phytochemical components of this plant showed various pharmacological and biological activity against certain chronic diseases like cancer, cardiovascular disease, immunosuppressive disease and gastrointestinal disorder. The different parts of this plant extract possess pharmacological activities like anticonvulsant, antioxidant, anti-inflammatory, antidiabetic, antidiarrheal, antihyperglycemic, anxiolytic, antidepressant, antihistaminic, antimicrobial, hepato protective, analgesic, immuno modulatory, cardio protective and antithyroid activities. The present review summarizes the information about botany, ethnopharmacology, phytochemistry, biological activities and insecticidal properties of *A. marmelos* plant.

Keywords: *Aegle marmelos*, botanical description, phytochemical, ethnopharmacology, coumarins, tannins and pharmacological activities

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INTRODUCTION

Plants have been used as a natural source of medicinal compounds since thousands of years. Bael (*Aegle Marmelos* (Linn), family Rutaceae, is also known as Bale fruit tree, is a moderate sized, slender, aromatic tree, 6.0 -7.5 m in height, and 90 to 120 cm in width, ascending to an altitude of 1200 meter in the western Himalayas ¹. *A. marmelos* plant and their plant products are used to cure and relief from physical and mental illness. These plants are used in traditional Chinese, Ayurveda, Siddha, Unani and Tibetan medicines. Ancient literature such as Rigveda, Yajurveda, Atharvaveda, Charak Samhita and Sushrut Samhita also describes the use of plants for the treatment of various health problems ². These plants are also used for the treatment of several medicinal properties such as an anticancer activity, antibacterial activity, antifungal activity, antidiabetic activity, antioxidant activity, hepatoprotective activity, haemolytic activity, larvicidal activity and anti-inflammatory activity etc and also used in treatment of diarrhea and dysentery. Leaves of *A. marmelos* used to cause infertility/abortion in women ³.



Figure 1: Leaves of *Aegle marmelos*

Taxonomic Classification ⁴:

Table 1: Taxonomic classification of *A. marmelos* L.

Taxonomy of <i>Aegle marmelos</i>	Vernacular names of <i>Aegle marmelos</i>
Kingdom: Plantae	English: Wood/Stone apple, Bengal Quince, Indian Quince
Subkingdom: Tracheobionta	Bengali: Bel, Shreefal
Super division: Spermatophyta	Hindi: Sir Phal
Division: Magnoliophyta	French: Oranger du Malabar
Class: Magnoliophyta	Indonesian: Mojo tree
Subclass: Rosidae	Javanese: Modjo
Order: Sapindales	Khmer: Banu
Family: Rutaceae	Latin: <i>Aegle marmelos</i>
Genus: <i>Aegle</i>	Malay: Pokok Maja Batu
Species: <i>Aegle marmelos</i>	Marathi: Kaveeth
	Nepali: Bel, Gudu
	Sanskrit: Shreephal, Bilva, Bilwa
	Tamil: Vilva Maram, vilva Pazham
	Telugu: Maredu
	Thai: Mapin, Matum, Tum
	Urdu: Bel
	Vietnamese: Mbau Nau, Trai Mam

Origin & Distribution ^{5,6}:

The Bael tree is originated from Eastern Ghats and Central India. The native place of *A. marmelos* is INDIA. *A. marmelos* is found growing along foothills of Himalayas, Bihar, Uttarpradesh, Jharkand, and Madhya Pradesh and it is also grown in some Egyptian gardens in Surinam and Trinidad. *Aegle marmelos* is widely distributed in India, China, Nepal, Sri Lanka, Pakistan, Bangladesh, Indonesia, Malaysia, Tibet, and Philippines and it also found almost in all the states of India.

Botanical Description ⁷:

Aegle marmelos is a slow-growing, medium sized tree, up to 25 -30 feet in height with short trunk, thick, soft, flaking bark, and has few spiny branches. The full botanical description of *A. marmelos* is given in Table 2

Table 2: Botanical Description of *A. marmelos L.*

Plant part	Morphological characters
Bark	The bark is brownish or grey in colour and it contains a no. of straight long spines.
Leaf	These leaves are trifoliate and having round base and pointed tip. Young leaves are light green & Matured leaves are dark green in color.
Flower	The flowers are greenish or yellowish in color and bisexual in nature.
Fruit	The Bael fruit is green in unripe stage and it changes to yellowish brown when ripen. It contains 15-20 orange pulp inside of the fruit.
Seed	The seeds are small, hard, flattened-oblong, bearing wooly hairs and each enclosed in adhesive sac.

Utilization of *A. marmelos*:

Every part of *A. marmelos* plant is utilized for general purpose and also medicinal purpose.

General uses:

- The wood is yellowish or grayish white, hard lustrous and aromatic. The wood is suitable for house building, cart construction, agricultural implements and cattle sheds ⁵.
- The twigs and leaves are used as fodder & the twigs are used to make tooth brushes or chew-sticks.
- In Siam, the shell of the fruit is used for scenting hair oil. On distillation, the rind of crops the essential oil known as Marmelle oil.
- The sweet aromatic fruit pulp is very nutritious, which is used for making Sharbat & also used as a substitute for clothes soap because it has detergent properties ⁸.

Ethanomedicinal uses:

It is well recognized plant whose various parts such as fruit, root, bark, leaves as well as flowers of *Aegle marmelos* have a high ethnomedicinal use. *Aegle marmelos* is used as carminative, anti-venom, astringent, and also used in thyroid-related disorders ⁹. It is also used as a cardiac stimulant, and also used to treat anaemia, fractures, swollen joints, pregnancy troubles, typhoid, coma, colitis, bleeding sores, and cramps ¹⁰. Among different parts, fruit is one of the important parts that can cure maximum no. of diseases. Roots are used for the treatment of fever, abdominal pain, anorexia, urinary troubles, hypochondriasis, melancholia and also used to cure cardiac malfunction. Leaves are used to lowers the high blood pressure, inflammation and it provides relief from menstrual problems and also provides relief from cough, cold, asthma, bronchitis, influenza and other similar respiratory disorders. Bael is used to control haemorrhoid's as the dose involves the intake of a combination of dried and powdered Bel leaves, dried ginger, carom seeds, and black pepper mixed in a glass of buttermilk or lukewarm water. Dried Bael leaves and pulp are used to restore appetite and eliminate helminths. Leaves are used as an astringent, laxative, digestive and febrifuge when fresh. They are also useful in ophthalmia, loss of hearing and inflammation. The unripe fruit is used for the curing of dysentery. The ripe fruit is also used as an astringent, appetizer, laxative, tonic, restorative, febrifuge ¹¹. Fruit powder of *Aegle marmelos* has an anti-proliferative and anti-cancer activity. A mixture of boiled rice water and unripe fruit pulp cures vomiting during pregnancy by taking 2 times per day. When the unripe fruit pulp mixed with milk and sugar used to cure urinogenital disorders. For the treatment of dysentery and abscess, half cooked unripe pulp mixed with sugar is essential. The leaf extract of *Aegle marmelos* is used to cure ophthalmia, ulcer and intestinal worms by intake of a day. *A. marmelos* Leaf juice having a number of medicinal importance especially for controlling diabetes. A number of ethno-medicinal uses of *Aegle marmelos* is detailed in table 3 ⁴.

Table 3: Ethnomedicinal uses of *A. marmelos* L.

Plant part	Ethnomedicinal uses
Leaf	Abscess, backache, eye complaints, abdominal disorders, vomiting, cut and wounds, ulcer, weakness of heart, cholera, diarrhoea, cardio tonic, hypoglycaemia, nervous disorders and acute bronchitis etc.,
Fruit	Astringent, diarrhoea, gastric troubles, constipation, laxative, tonic, dysentery, brain and heart tonic, ulcer, antiviral, intestinal parasites, gonorrhoea, epilepsy.
Root	Dog bite, gastric troubles, heart disorders, intermittent fevers, antiamoebic, hypoglycaemic, rheumatism.
Bark	Stomach disorder, intermittent fevers, heart disorder.
Seed	Febrifuge.
Flower	Expectorant, epilepsy.

Phytochemical composition:

A. marmelos having a variety classes of compounds like alkaloids, cardiac glycosides, saponins, steroids, coumarin's, terpenoids, phenylpropanoids, tannins, polysaccharides and flavonoids which are obtained from the different parts of tree.

Alkaloids¹²:

The alkaloids comprise the largest single class of secondary plant substances. Various alkaloids are Aeglin, aegelenine, dictamine, fragrine (C₁₃H₁₁O₃N), O-methylhalfordinine, isopentenylhalfordinol (15), N-2- [4-(3', 3'-dimethylallyloxy) phenyl] ethyl cinnamide, N-2-hydroxy-2- [4-(3', 3'-dimethylallyloxy) phenyl] ethyl cinnamide, N-2-hydroxy-(4-hydroxyphenyl) ethyl cinnamide. O-(3, 3- dimethylallyl) halofordinol, N-2-ethoxy-2-(4-methoxy phenyl) ethyl cinnamide, N-2-methoxy-2- [4-(3', 3'- dimethylallyloxy) phenyl] ethylcinnamide, N-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamide.

Terpenoids^{13,14}:

The essential oil of *A. marmelos* leaves were studied very much extensively. Alpha- phellandrene was found to be the common constituent of essential from the leaves, twigs and fruits. Alpha phellandrene (56%) and p-cymene (17%) were obtained from leaf oil. later P-Menth-1-en-3,5-diol was isolated and characterised from *A. marmelos* leaves. Limonene is the main constituent of *Aegle*.

Coumarins¹⁵:

Marmelosin, marmesin, imperatorin, marmin, allomperatorin, methyl ether, xanthotoxol, scopoletin, scoparone, umbelliferone, psoralen and marmelide are observed.

Phenylpropanoids¹⁶:

These are naturally occurring phenolic compounds, which are having an aromatic ring to which 3C sidechains are attached. The phenylpropanoids consists Hydroxycoumarins, phenylpropenes and lignans. Marmesin was established as a new compound from leaves, heartwood and root.

Flavonoids¹⁷:

It includes Rutin, Flavone, flavan-3-ols, flavone glycosides.

Polysaccharides^{18,19}:

Galactose, arabinose, uronic acid and L-rhamnose are obtained on hydrolysis.

Seed oil²⁰:

Seed oil is bitter and it consists palmitic, stearic, oleic, linoleic and linolenic acid.

Tannins¹⁸:

The maximum tannin content in *A. marmelos* fruit was recorded in the month of January. 9% of tannin in the pulp of wild fruits is less in cultivated type. Tannin is also present in leaves as skimmianine, it is also named as 4, 7, 8-trimethoxyfuro, quinoline.

Carotenoids:

The carotenoids are the Marmelosin, skimmianine and umbelliferone which are therapeutically active principles of *Aegle marmelos*. Minor constituents like ascorbic acid, sitosterol, crude fibres, tannins, α -amyrin, carotenoids, and crude proteins are also present. Roots contains psoralen, xanthotoxin scopoletin and tembamine.

Compounds such as praealtin D, trans-cinnamic acid, 4- methoxy benzoic acid, betulunic acid and montanin have also been observed from the *A. marmelos* ¹².

A large number of bioactive compounds have been isolated from various part of this plant, a few of them have been presented in Table 4 ²¹.

Table 4: Phytochemical Constituents of *Aegle marmelos L.*

Parts of plant	Chemical constituents	Therapeutic effects
Leaf	Skimmiamine, Aegelin, Lupeol, Cineol, Citral, Citronellal, Cuminaldehyde, Eugenol, Marmesin	Anti-cancer, cardio active, Anti-inflammatory, Anti-septic, Antiallergic etc.
Bark	Immature- Marmin, Skimmiamine, Mature- Fagarine	Abortifacient, Anti-ulcer, antidiarrheal
Unripe fruit	Tannin	Astringent
Fruit	Marmelosin, Luvangetin, Aurapten, psoralen, Marmelide	Cardio-protective, anti-ulcer, Heartbeat inhibitor, Antispasmodic, Anti-diarrheal

Nutritional Value ¹⁰:

Nutritional Value of Bael plant is a rich source of proteins, carbohydrates, vitamins, and minerals. The Bael plant contains vitamins such as carotene, thiamin, riboflavin, and niacin and minerals like calcium, iron, phosphorus. Plant shows a variety of health benefits due to the presence of both macro and micronutrients such as vitamins, organic compounds including tannins, alkaloids, polyphenols, terpenes, fiber, protein, and oil. Bael pulp is a rich source vitamin C (ascorbic acid). The fruit pulp is blended with 30% sugar, and dehydrated powder is used for the preparation of cold drink or soft squash. Bael fruit is used for the preparation of toffee by combination of the pulp with sugar, glucose, skim milk powder, and hydrogenated fat. Bael fruit helps to destroy worms in the intestine and it is also recommended as a remedy for chronic dysentery. Fresh juice of leaves or flowers decreases the appetite while an infusion of the flowers mixed with sugar and milk is used as a cooling drink. Milk and sugar added to fruit juice make it more edible. The pulp of Bael fruit

is used for making squash, nectar, jellies, marmalades, and candies. Mucilage from unripe seeds of Bael fruit is used as adhesive and glue. A gum-like thick substance collected from tree trunk and branches of Bael trees is used to make Feronia gum. The Bael dry powder is mixed with mustard oil in (1:2) used for the treatment of burn and applied externally. This is commonly used for curing of diarrhea and dysentery. Bael fruit is commonly recommended for treatment of peptic ulcer or piles, digestive problems, and to beat heat stress. Bael fruit juice is commonly recommended for purification of blood and to remove toxins from liver and kidneys. It also acts as an immune modulator and atone defense against toxins. *A. marmelos* is a good source of β -carotene, thiamine, and riboflavin, which are known as liver health boosters. Bael fruit also functions as an ingredient in cardiac tonics.

REPORTED ACTIVITIES OF AEGLE MARMELOS:

A. marmelos is one of the most widely used medicinal plant in the family Rutaceae. In recent history this plant is reported for various medicinal properties.

Antioxidant Activity:

Antioxidants are the compounds which are having free radicals scavenging activity and also used to protect the cells from free radical mediate oxidative stress. The antioxidant compounds are derived from natural sources such as plants. Antioxidant activity of these plants is due to the presence of flavones, isoflavones, flavonoids, anthocyanin, coumarin lignans, catechins and isocatechins. *A. marmelos* plays an important role in cytoprotection as well as protection against pro-oxidant-induced membrane damage. The antioxidant effect of aqueous extract of *A. marmelos* leaves carried out by using male albino rats. Glucose, Urea and glutathione-S-transferase in plasma, glutathione (GSH) and malondialdehyde (MDA) levels in erythrocytes, DT-diaphorase, superoxide dismutase, and catalase in the lung were estimated in all the groups of animals at the end of 4 weeks. These changes occurred in body fluids of drug-catabolism. The blood glucose levels and MDA levels are decreased at the end of 4 weeks & then GSH levels in Erythrocytes are increased in group treated with *A. marmelos* as compared to diabetic rats^{22,23}. Leaf extract also protects antioxidant defence system and restore histological changes of pancreatic β -cells in STZ-induced diabetic rats²⁴. Antioxidant activity and free radical scavenging activity of *Aegle marmelos* is compared in between ripe and unripe fruit. The results of enzymatic antioxidants increased in ripe fruit when compared to unripe fruit extract (except glutathione peroxidase). The percentage of free radical inhibition is high in unripe fruit than that of the ripe fruit²⁵. Screening of fruit pulp of *A. marmelos* methanolic and aqueous extract for antioxidant activity by DPPH radical scavenging method, reducing power assay, nitric oxide scavenging assay, superoxide radical

scavenging assay, ABTS radical scavenging assay and H₂O₂ radical scavenging assay. Both aqueous and alcoholic extract exhibits good antioxidant activity²⁶.

Antimicrobial Activity:

A. marmelos has been traditionally used for the treatment of various infectious diseases like Bacteria, fungi and viruses to inhibit the broad range of pathogenic microorganisms. The antimicrobial activity of the leaves of *A. marmelos* was observed by agar well diffusion method. The aqueous, petroleum ether and ethanol extract of the leaves of *Aegle marmelos* exhibits an efficient antimicrobial activity against multi resistant strains of *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Streptococcus pneumoniae*, *Salmonella typhi*, *Klebsiella pneumoniae* and *Proteus vulgaris*. The ethanolic extract showed an activity against *Penicillium chrysogenum* and the petroleum ether and aqueous extract shows an activity against *Fusarium oxysporum*²⁷. The methanol extract of bilwa has high antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Escherichia coli*, *Salmonella paratyphi A* and *Salmonella paratyphi B*. The hexane, cold methanol, hot methanol and ciprofloxacin extracts showed high antimicrobial activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Micrococcus luteus*, *Enterococcus faecalis* and *Streptococcus faecalis*³. The antimicrobial activity against gram-negative strains shows higher microbial activity than that of gram-positive strains²⁸. The chemical constituents like Cuminaldehyde and Eugenol which are present in leaves *Aegle* shows high antimicrobial activity²⁹.

Antibacterial Activity:

Various extracts of *A. marmelos* leaves, roots and fruits have been reported to be active against many bacterial strains. Bacteria are the most versatile unicellular pathogens, which are normally transmitted through soil, water, air and food and cause diseases in human beings and animals. Such types of diseases could be treated with various natural products like *Aegle marmelos*. Different extracts of *Aegle* showed antibacterial activity against *Micrococcus glutamicus*, *Streptococcus faecalis*, *Staphylococcus aureus*, *S. pyogenes*, *Bacillus stearothermophilus*, *Micrococcus luteus*, *E. coli* and *Pseudomonas denitrificans*. The antibacterial activity of the different extracts was evaluated by agar well diffusion method. Various extracts like hexane, cold methanol, hot methanol and ciprofloxacin extracts shows high antibacterial activity against different organisms that are *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Micrococcus luteus*, *Enterococcus faecalis* and *Streptococcus faecalis*³⁰. Leaf extracts have showed an activity against *Escherichia coli*. The essential oil obtained from the leaves exhibited activity against *Aeromonas sp.*, *Escherichia coli*, *Pseudomonas salanacearum* and *Xanthomonas vesicatoria*. The ethanolic

extract of the root has shown activity against *Vibrio cholerae*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus*. The ethyl acetate extract of the plant exhibits an activity against *Vibrio cholerae*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Pseudomonas putida* and *Bacillus anthracis* ³¹. Methanol and aqueous extracts of *Aegle* fruits have shown strong activity against multi drug resistant *Salmonella typhi*. The methanol extract showed high antibacterial activity than that of the other extracts ³². The minimum inhibitory concentration (MIC) value of the methanolic extract is around 256 µg/ml. The unsaponifiable matter of the seed has shown considerable in vitro activity against *Escherichia coli*, *Salmonella typhi*, *Salmonella paratyphi*, *Proteus vulgaris*, *Streptococcus faecalis*, *Vibrio cholerae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. Both the oil and the unsaponifiable matter of the seed have also been found to be active against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella aerogenes*, *Salmonella typhi*, *Salmonella paratyphi*, *Staphylococcus aureus*, *Erwinia carotovora*, *Pseudomonas solanacearum*, *Xanthomonas citri*, and *Xantha malvacearum* ^{33,34}. So, that it is evident that the *Aegle* has antibacterial activity and the mechanism of action may be the blockage of protein synthesis either at transcription or translation level and/or peptido-glycan synthesis at membrane level. The antibacterial activity of the leaf extracts was observed due to the presence of cuminaldehyde and eugenol because these compounds have already shown their activities against various bacterial strains ³⁵.

Antifungal Activity:

The antifungal activity was performed by tube dilution MIC method and also This activity was performed by using 21 days old culture of dermatophytic fungi with distilled water. The suspension was adjusted spectrophotometrically to an absorbance of 0.0600 at 450 nm. Vulnerability testing was executed by micro dilution method. Potent antifungal activity was found when *A. marmelos* leaf extract was applied against *Trichophyton mentagrophytes*, *T. rubrum*, *Microsporum canis*, *M. gypseum*, *Epidermophyton floccosum* ⁴. Decoction of the fruit exhibited an activity against *Aspergillus niger*, *Aspergillus fumigatus*, *Candida albicans* and *Staphylococcus aureus* and the MIC results for the above particular organisms were 19.5 µg/ml, 39 µg/ml, 625 µg/ml and 1.25 mg/ml ³⁶.

The essential oil isolated from the leaves of *Aegle* has proved its antifungal activity against many animal and human fungi like *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum*, *M. audouinii*, *M. cookei*, *Epidermophyton floccosum*, *Aspergillus niger*, *A. flavus*, and *Histoplasma capsulatum*. The unsaponifiable matter of the seed of *Aegle* has exhibited an in vitro

activity against various fungi like *Trichophyton rubrum*, *T. terrestre*, *Epidermophyton floccosum*, *Aspergillus fumigatus*, *A. niger* and *A. flavus*. The ethanolic extract of the root has exposed an activity against *Aspergillus fumigatus* and *Trichophyton mentagrophytes*. The germination of any spore (i.e., bacterial or fungal) is connected to Ca^{2+} – dipicolonate and/or free Ca^{2+} ions availability in the medium as well as within cytoplasm of microbes. This Ca^{2+} ion uptake and utilization by spore is one of the important factors that determine whether the spore will germinate or remain dormant. The essential oil from the *Aegle* leaves may interfere with the Ca^{2+} – dipicolonic acid metabolism pathway and possibly inhibit spore germination. This is the possible mechanism of the protective role of *Aegle* leaf oil against fungal infection³¹.

Antiviral Activity³¹:

Virus is considered as a living substance inside the host body and as a non- living outside the host body. It leads to seasonal outbreak and does not respond properly to most of the synthetic drugs. Virus is the smallest pathogen with its dual form: a living entity in inside the host body and non-living entity form in outside of the host body. The in vitro antiviral activities of various parts of the bael tree have been evaluated for their efficacy against human coxsackie viruses B1-B6. The IC₅₀ of leaves, stem and stem bark, fruit, root and root bark and the pure compound marmelide are 100-1000, 500-1000, 250-500 and 62.5 µg /ml, respectively, and also the IC₅₀ of ribavirin is standard antiviral agent, is 2000 µg/ml for the same viruses and at the same time period¹⁰. Marmelide is the most active virucidal agent interfering with the initial events of its replicative cycle. It seems that *Aegle* has antiviral activities in the early stages of viral replication with minimum host cytotoxicity in contrast to modern virucidal chemotherapeutic agents (i.e., ribavirin), which acts in the later stages of viral replication and also have potent side effects. The effect of various extracts of *Aegle* also acts on the late protein synthesis were studied to evaluate its degree of potentiality as an antiviral agent. The 50% ethanolic extract of the fruits has shown antiviral activity against Ranikhet disease. The fruit extract has exhibited interferon-like activity against the same virus but not showed an activity against vaccinia virus. So that the *Aegle* has better virucidal activity.

Antidiarrheal activity:

Antidiarrheal activity is one of the most important medicinal properties of *A. marmelos* and it is extensively used to control chronic diarrhea and dysentery. Recently, several in vitro and in vivo studies are conducted to confirms the antidiarrheal activity in *A. marmelos*. The in vitro antidiarrheal activity in dried fruit pulps of *A. marmelos* was performed. Antidiarrheal activity was conducted by MIC method against the causative organisms of diarrhoea³⁷. Both root and leaf extracts of *Aegle* shows gastroprotective and antidiarrheal activities against oil induced diarrhea in

animal models. Unripe fruit reduces rapid flush and limit sensation to defecate, blood, and mucus. The dry powdered leaves and fruit pulp is specially administered in sub-acute, chronic, and amoebic dysentery. The unripe fruit is also baked with jaggery or brown sugar. Juice of green fruit pulp is used to have relief from acute dysentery. Fine fruit powder is taken with a cold water stops blood release and continue stools to make it more feculent and solid. The mucus also evaporates after continued use of Belgiri. It is one of most important remedy under chronic dysenteric conditions characterized by alternate diarrhea and constipation. Methanolic extract of *A. marmelos* found active against castor oil-induced diarrhoea in mice ¹⁰. The ethanolic extract exhibits good activity against *Shigella boydii*, *S. sonnei* and *S. flexneri*, moderate against *S. dysenteriae*. Crude aqueous extract of unripe fruits of *A. marmelos* was separated for causative agents of diarrhea. The extract was detected for antibacterial activity, anti-giardial activity and antirotaviral activity and also the extract exhibits an inhibitory activity against *Giardia* and rotavirus whereas viability of none of the six bacterial strains tested was affected ³⁸.

Antihistaminic Activity ³⁹:

Skimmianine is a compound of quinoline alkaloid which is isolated from the roots of *A. marmelos*. In this study the effects of skiamminine acts on the release of histamine from rat mast cells are tested. The study was conducted by using two cell lines that are rat basophilic leukaemia (RBL-2H3) cell line and rat peritoneal mast cells (RPMCs). DNP24-BSA, thapsigargin, Ionomycin mixtures 48/80 were used as an inducer for the release of histamine from rat mast cells. The compound skimmiamine highly inhibits the release of histamine by acting on histamine H1 receptor from RBL-2H3 cells induced by DNP24-BSA, thapsigargin and ionomycin.

Hepatoprotective Activity ⁴:

A. marmelos leaf produces hepatoprotective effect for liver injury in albino rats due to alcohol consumption. Rats are injected with bacterial suspension at a dose of 5×10^6 CFU/0.1 ml through intraperitoneal route. Then the animals were treated with *Aegle marmelos* alcoholic extract for 15 days in functional saline at a concentration of 100 mg/kg of body weight. After 15 days, the animals were fasted for 12 hrs and then scarified under mild chloroform anaesthesia. Bloods of animals are collected for separation of serum and the organs are excised and washed in ice cold saline until homogenized. Biochemical parameters like SGOT, SGPT, alkaline phosphate, total bilirubin and protein levels were analyzed. Estimation of blood glutathione performed using DTNB. some studies which are performed on four groups of animals by administration of 30% ethyl alcohol for 40 days with control group of *Aegle marmelos* leaves. The induced rats were

administered with the leaves of *A. marmelos* for 21 days. This experiment results indicates that *Aegle marmelos* leaves have excellent hepatoprotective effect.

Cardioprotective Activity ^{40,41}:

The leaf extract of *Aegle* has preventing effects in Isoprenaline induced myocardial infarction in albino-wistar rats. It shows significantly increases the levels of creatine kinase and lactate dehydrogenase enzymes and also decreases significantly in the heart of isoprenaline-treated rats. *Aegle marmelos* is used as a cardiac depressant and in palpitation has also been observed ⁴⁰. Fresh fruit juice of *Aegle* administered in different dilutions are used for cardiogenic activity. The present studies confirm that *Aegle* has better cardiogenic activity than Digoxin ⁴¹.

Anticancer activity:

Cancer is 2nd main cause of death in both men and women in developed and developing countries. The fruit extract of *Aegle* is used to improve the immune system that will finally rise the anticancer activity of a body. Preclinical studies exhibit that *A. marmelos* leaf extracts were active in inhibiting the growth of organisms like leukemic K562, T-lymphoid Jurkat, B- Lymphoid Raji, erythroleukemic HEL, melanoma Colo38, and breast cancer cell lines MCF7 and MDAMB-231. Different Experiments have shown that the phytochemicals such as lupeol, eugenol, citral, cineole and d-limonene which are present in *A. marmelos* shows antineoplastic effects ⁴².

The hydroalcoholic extract of *Aegle* leaves has revealed anticancer effect in the animal model of Ehrlich ascites carcinoma. Administration of the extract (400 mg/kg) has shown the highest antitumor effect. The plant extract exhibits cytotoxicity against tumour cell lines in sea urchin eggs assay, brine shrimp lethality assay and methyl thiazolyl tetrazolium (MTT) based assay. The extract also possesses anti-proliferative activity on MCF7 and MDA-MB231 breast cancer cell lines. Initiation of apoptosis occurs due to the presence of skimmianine in the leaf extract that kills the tumour cells ³¹.

Wound Healing Activity ⁴³:

Aegle marmelos leaves are mostly used for the treatment of wound. The methanolic extract of *Aegle marmelos* was administered on topical as well as intraperitoneal administration was studied under two types of wound models that are excision and incision wound model in rats. Both the injection and ointment produces same response in excision as well as incision wound type was tested. In the excision model the extract which is used in treated wounds were found to epithelialize faster and also the rate of wound contraction was higher when compared to control wounds. The extract also facilitates the healing process by increasing the tensile strength in incision wound type. Then the results were also compared with the standard drug nitrofurazone.

Antifertility Effect ⁴⁴:

The antifertility effect of the aqueous extracts of leaves of *Aegle marmelos* was performed in male Albino rats. The rats were administered with aqueous extracts (250 mg/kg body weight) of *Aegle marmelos* leaves for 45 days and then the Treatment was observed by the reduction in the weights of testis, epididymis and seminal vesicle. The extract also results in reduction of testicular sperm count, epididymal sperm count, motility and abnormal sperm count.

Antidiabetic Activity ¹⁰:

Leaf extract of *A. marmelos* is an important medicine for the treatment of diabetes. It also enhances the ability to utilize the external glucose load in the body by stimulation of glucose uptake similar to insulin. *Aegle* leaf extract significantly decreases the levels of blood urea and cholesterol and also decreases oxidative stress in experimental diabetic animals, it is indicated by significant reduction in lipid peroxidation, conjugated diene and hydroperoxide level and increased levels of various enzymes like superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels in serum as well as liver. Leaf extract in *A. marmelos* shows the anti-diabetic and anti-hyperlipidaemic effect of allopolyherbal formulation in oral glucose tolerance test and STZ-induced diabetic rat model. It significantly enhances glycaemic control, protects the pancreas from degeneration, and shows antioxidant and hepatoprotective effects. It contains umbelliferon- α -D-glucopyranosyl-(2(I) \rightarrow 1 (II))- α D-glucopyranoside that cut down extra glucose level in STZ induced diabetic rats. *A. marmelos* also shows ameliorative effects in alloxan induced early-stage diabetic nephropathy and cardiomyopathy in rats. *A. marmelos* extract also inhibits aldose reductase enzyme and shows its protective role in diabetic cataract. It also shows in vitro inhibitory effects on intestinal α -glucosidase and pancreatic α -amylase. The leaf extract also prevents secondary complications in STZ-induced diabetic rats due to the presence of limonene as a potent anti-glycating agent. Bark extract shows hypoglycaemic and β -cells regenerative effects in STZ-induced diabetic rats. *A. marmelos* leaf extract improves tissue antioxidant defense system and restores histological changes of pancreatic β -cells in STZ-induced diabetic rats. It also restores haemostatic function in STZ-diabetic rats and also acts as an anti-hyperglycaemic and anti-dyslipidemic agent. Both the extracts and chemical constituents of *Aegle* are used for preparing herbal drugs for the treatment of ischemic heart disease in patients with diabetes. The plants of green leafy porridges are used to control hypo and hyperglycaemic responses. Leaf extract of *Aegle* also decreases the muscarinic M1 receptor gene expression in the cerebral cortex of STZ-induced diabetic rats. Leaf extract shows antihyperlipidemic activities and anti-diabetogenic properties and lowers down diabetic effects in STZ-induced diabetes in experimental rats. The

chloroform extract of *A. marmelos* established anti-diabetic anti-glycating and antioxidant activity, effectively preventing kidney damage and the establishment of cataracts. Hence, the plant is used for management of Type 2 diabetes.

Miscellaneous Properties ¹²:

Leaves of *Aegle marmelos* are used for the treatment of jaundice, leucorrhea, conjunctivitis, and also wounds and thyroid related disorders. *Aegle marmelos* acts as an astringent and carminative and also acts as cardiac stimulant. It is also used in treatment of irritable bowel syndrome, snake bite, acute shigellosis, and in gonorrhoea.

Toxicity studies:

Aegle marmelos has various medicinal properties and also utilized as nutritional food. However, the leaves of *A. marmelos* is not administered in pregnant or breastfeeding women because it has been traditionally used to induce abortion and to sterilize women. Recently, leaves of *A. marmelos* were studied as acute and subacute toxicity properties. The different extracts of the *A. marmelos* leaves were tested in Wistar albino rats for the LD50 values of acute and subacute toxicity effects. The results were observed that the LD50 value of the different extracts, was administered from 1300 mg to 1700 mg/kg body weight of various groups of animals. There were no changes observed in the histopathological studies after 50 mg/kg body wt. (daily, 14 days) ⁴⁵. Dried fruit pulp of *A. marmelos* was screened for its topological profile. Ethanolic extract of *A. marmelos* dried fruit pulp was screened for the acute oral toxicity test in Swiss albino mice at 550 and 1250 mg/kg body weight. At these concentrations test extract did not showed any sign of toxicity. No change in the behaviour and physiological activity was observed in mice during the 14 days of experiment. The results concluded that LD50 values of the test extract is more than 1250 mg/kg body weight ³⁷.

CONCLUSION:

From this review, *Aegle marmelos* is an important medicinal herb and extensively used in Ayurveda, Siddha and other medicinal systems. The different parts of this plant such as leaf, fruit, seed, bark and root are used to cure a variety of diseases. The *A. marmelos* contains Antioxidant, Antibacterial, Antifungal, Antidiarrheal, Antidiabetic, Cytoprotective, Hepatoprotective, Antifertility, Anticancer, Antiviral and Wound Healing properties. Number of biologically active compounds are isolated from various parts of *A. marmelos*. The isolated compounds are Alkaloids, Terpenoids, Vitamins, Coumarins, Tannins, Carbohydrates, Flavonoids, Fatty Acids, Essential Oils and some other miscellaneous compounds. This review mainly focused on several phytochemical and reported pharmacological studies of *A. marmelos*.

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